IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of : Attorney Docket No.: 2503-A

Cindy A. Jacobs and Craig A. Smith

Serial No.: 08/385,229 Group Art Unit: 1806

Filed: February 8, 1995 Examiner: Nisbet, T.

For: METHOD OF TREATING TNF-DEPENDENT INFLAMMATION USING TUMOR NECROSIS FACTOR ANTAGONISTS

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF VIRGINIA PRICE, PH.D., UNDER 37 C.F.R. 1.132

Sir:

I, Virginia Price, Ph.D., do hereby declare and state:

1. That I received a Ph.D. degree from Oregon State University in Microbial Genetics. Since 1984, I have been engaged in research related to the expression of recombinant proteins. I was until recently the Director of Gene Expression and Fermentation at Immunex Corporation, and am currently a Research Investigator in the Department of Cell Sciences. A copy of my curriculum vitae is attached as Exhibit A.

2. That I have read and understand the above-referenced patent application and the Office Action dated November 24, 1995 in connection thereto. The Examiner stated in the Office Action that the art is sufficiently unpredictable that the making of the claimed proteins having deletions or substitutions between amino acids 3-163 would require more than routine experimentation. As a person having ordinary skill in the art, I believe the Examiner's statements regarding the disclosure in the specification are not correct.

3. That once the nucleotide sequence of a DNA encoding a protein is known, it is a matter of routine experimentation for those of ordinary skill in the art of molecular biology to prepare additional DNA sequences similar to the known DNA sequence, but that contain substitutions or deletions in the nucleotide sequence. It is also a matter of routine experimentation to determine the effect of such changes on the biological activity of a peptide expressed from an altered DNA sequence.

4. That methods of making changes in nucleotide sequences are well-known in the art of molecular biology. The procedures described in the instant application at page 6, lines 4 et seq. are routine and would result in the generation of what are termed therein as "bioequivalent analogs of TNFR." These procedures and methods include, for example, site-directed mutagenesis (described at page 8, lines 5-11), in which specific nucleotide changes are made at specific residues; oligonucleotide synthesis (page 6, lines 4-5); and deletion of sequences, for example by using restriction enzymes. Such methods can be used to generate conservative substitutions as defined in the application, or to remove or replace cysteine residues, to delete terminal or internal residues or sequences as described in the application.

5. That once the analog of a protein is made using the procedures described in the application, and as I have outlined in paragraph 4 above, the protein can be expressed and purified following conventional methods and the detailed procedures set forth in the application. Once expressed and purified, the it is considered routine methodology and practice to perform assay(s) to determine whether or not the analog protein possesses activity. Such assays for determining protein activity are well-known in the art at the time the application was filed. These include a standard binding assay wherein thr TNFR analog would be assayed for its ability to bind TNF (see page 19, lines 27-29 of the application). Such well-known binding assays include more specifically, a TNFR membrane binding assay, a TNFR solid phase binding assay, a TNFR whole cell binding assay, and a binding assay for soluble TNFR. Such assays are considered routine experimentation and could have been easily prepared and performed by a person that had ordinary skill in the art of molecular biology.

6. That it therefore would have been a matter of routine experimentation to prepare and express TNFR analogs from DNA that contains changes in the nucleotide sequence, and determine whether or not the analog expressed from the altered DNA sequence exhibits activity in one of the described assays. I further declare that the ordinary skilled molecular biologist is likely to prepare and test more than one mutein in one 'experiment' (usually from about four to about ten muteins) which would take approximately two to four weeks to conduct. The length of time it takes to complete such an experiment is dependent on the resources available and the length of time required for the biological systems to yield results (i.e., the time required for transformed/transfected cells to grow and express a protein, the time required for other cells to proliferate in response to the protein, etc.). The length of time is not due to any requirement for extraordinary skill on the part of the molecular biologist, or to the requirement for unusual reaction conditions or to the use of any special equipment.

7. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Virginia Price, Ph.D. May 21, 1996

Virginia Price, Ph.D. Date